

## Hypomagnesaemia in chronic, stable asthmatics: prevalence, correlation with severity and hospitalization

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*Hypomagnesaemia in chronic, stable asthmatics: prevalence, correlation with severity and hospitalization. O.S.B. Alamoudi. ©ERS Journals Ltd 2000.*

**ABSTRACT:** Magnesium (Mg) deficiency is associated with airway hyperreactivity, wheeze and impairment of lung function. The prevalence of hypomagnesaemia, and its effect on asthma is unclear. Therefore, this prospective study was undertaken to evaluate the prevalence of low serum Mg level, to correlate whether hypomagnesaemia (serum Mg level  $<0.74$  mmol·L<sup>-1</sup>) is associated with severity of asthma and increased frequency of hospitalizations in chronic, stable asthmatics.

Ninety-three chronic stable asthmatics, who were on regular follow-up in an asthma clinic, were studied. On attendance to the asthma clinic, each subject was interviewed and clinically evaluated. The serum Mg level (normal 0.74–1.2 mmol·L<sup>-1</sup>), as well as the severity of asthma was measured. The medications used were recorded. The total number of hospitalizations due to asthma exacerbation was scored for the last three months that preceded the date of measuring the serum Mg level.

Twenty-five patients (27%) had a low Mg level with a mean  $\pm$ SD of  $0.69 \pm 0.04$  mmol·L<sup>-1</sup>, while 68/93 (73%) had a normal Mg level ( $0.82 \pm 0.08$  mmol·L<sup>-1</sup>). The number of hospitalizations in asthmatics with low Mg levels was 10/25 (40%), compared to 8/68 (12%) ( $p < 0.01$ ) in asthmatics with normal Mg levels. Multiple logistic regression analysis showed that severe asthma was the only factor associated significantly with hypomagnesaemia ( $p = 0.04$ ). No effect was observed for inhaled  $\beta$ -agonist, inhaled steroid or theophylline therapy on serum Mg level.

To conclude, hypomagnesaemia is common in chronic asthmatics. Chronic asthmatics with low Mg tend to have more hospitalizations than chronic asthmatics with normal Mg. Hypomagnesaemia was also associated with more severe asthma.

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Hypomagnesaemia has been suggested to be associated with increased incidence of wheeze, airway hyperreactivity, and impairment of lung function [1, 2]. The mechanisms of action of magnesium (Mg) on respiratory airways are multiple and include relaxation of airways smooth muscle, bronchodilatation, anticholinergic effect, and stabilization of the mast cells [3–5]. The prevalence of hypomagnesaemia in chronic asthmatics is unclear. One early report found a significant difference in serum Mg levels between asthmatics and the general population [6]. However, recent studies in acute and chronic asthma have shown no significant difference of serum Mg levels in asthmatics and nonasthmatic control subjects [7, 8]. In one study, it was found that measurement of serum Mg was not a reliable predictor for determining the severity of bronchial asthma (BA) [8]. Most of the previous studies on Mg [9–15] mainly concentrated on the use of Mg sulphate as a bronchodilator in acute asthma, with conflicting results. Recently, there has been growing evidence that low Mg intake may also play a role in the aetiology of asthma [16, 17]. The occurrence of hypomagnesaemia in asthmatics was not fully explained, but it was partly attributed to the increased urinary excretion of Mg, secondary to therapy used ( $\beta$ -agonist, steroids, and xanthines) for management of asthma [18–21]. Although

hypomagnesaemia has been reported in asthmatics, its prevalence in chronic asthmatics and its association with an increased number of hospitalizations or with severity of asthma is unknown.

The aims of this study were to detect the prevalence of hypomagnesaemia in chronic asthmatics and to assess whether chronic asthmatics with low Mg levels have a higher incidence of hospitalization. In addition, hypomagnesaemia is associated with severity of asthma and whether the therapeutic agents used in the management of chronic asthma have an effect on serum Mg level was also assessed.

### Materials and methods

The study was approved by the human ethics committee of King Abdulaziz University Hospital (KAUH), and carried out in strict compliance of their policy. It was conducted from July 1997–June 1998 in the outpatient asthma clinic at KAUH. Laboratory tests were carried out in the Biochemistry Dept at KAUH.

Ninety-three consecutive chronic stable asthmatics on regular follow-up in the asthma clinic were studied. Patients were diagnosed according to the American Thoracic Society Criteria [22]. Diagnosis was based upon clinical

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history, reversibility of forced expiratory volume in one second (FEV<sub>1</sub>), or peak expiratory flow (PEF) >15% and diurnal variations of peak expiratory flow rate >20%. The inclusion criteria were: signed consent form, age ≥14 yrs, nonsmokers, and no history of renal disease, diabetes, hypertension, cardiac disease, diarrhoea, alcohol abuse, diuretic use or current pregnancy. Hospitalizations were taken into account only if their sole reason was an asthma exacerbation.

Chronic asthmatics, who accepted to take part in the study were interviewed, clinically evaluated, and their PEF measured. A questionnaire that included the patient's age, sex, duration of BA, nocturnal symptoms, and number of hospitalizations (if any) was obtained from each subject and checked against their hospital notes.

Score for drug therapy according to ROLLA *et al.* [19] with modifications was assigned to each patient according to inhaled β-agonist use (1=< once per day, 2=every day, 3=> recommended dose; inhaled corticosteroids 1=use, 2=no use irrespective of duration of therapy; theophylline 1=use, 2=no use; and oral steroid 1=use, 2=no use).

The severity of chronic asthma while on therapy was graded into mild, moderate, and severe according to the international consensus report on diagnosis and management of asthma [23]. Severity of asthma was measured according to the patient's symptoms and PEF measurements. Mild asthma was diagnosed if intermittent symptoms were < once per week; nocturnal symptoms were < twice per month, asymptomatic between exacerbations, PEF >80% pred; and PEF variability <20%. Moderate asthma was diagnosed if nocturnal asthma symptoms were > twice per month, exacerbations >1–2 times per week, PEF 60–80% pred, and PEF variability was >30%. Severe asthma was diagnosed if continuous symptoms, frequent nocturnal asthma and frequent or life-threatening exacerbations, PEF <60% of pred, PEF variability >30%.

The total number of hospitalizations in asthmatics was scored for the last three months that preceded the date of measuring the serum Mg level. In asthmatics with hospitalization (n=18), the date of discharge from the hospital was recorded for each one. The measurement of serum Mg level was only done on the sixth week onwards after discharge from hospital to avoid any effect of therapy (nebulized β-agonists and *i.v.* steroids) on their serum Mg levels. Hospitalizations were scored when the sole reason for admission was an acute exacerbation of asthma. All asthmatics with hospitalization were hospitalized once during the last three months.

In the asthma clinic, serum Mg, potassium (K), calcium (Ca), phosphorus (P), albumin, urea, and creatinine levels were measured for each subject. Serum Mg levels were measured using an atomic absorption spectrophotometer (Hitachi 917; Hitachi, Tokyo, Japan). The normal serum Mg value measured in the laboratory was 0.74–1.2 mmol·L<sup>-1</sup>. Hypomagnesaemia was considered to be present if serum Mg level <0.74 mmol·L<sup>-1</sup>. Measurements of PEF were carried out using Wright's peak flow meter (Ferraris Medical Ltd, Edmonton, London, UK).

#### Data management and statistical analysis

Data were entered in a data base file and scrutinized for outliers. The statistical analysis was done using SPSS

statistical package (SPSS-PC, 444N. Michigan Avenue, Chicago, Ill., USA). Frequency distributions were compared using the chi-square test or Fisher's exact test. The unpaired t-test and analysis of variance (ANOVA) were used to compare mean values. Multiple logistic regression analysis was performed to adjust for the confounding variables and to identify important risk factors associated with hypomagnesaemia. Confidence intervals and tests of significance were computed based on maximum likelihood estimation of the logistic parameters. For all tests a p-value of <0.05 was considered significant.

#### Results

A total of 93 chronic stable asthmatics were studied. They were divided into 68 chronic asthmatics with normal serum Mg with a mean±SD of 0.82±0.08 mmol·L<sup>-1</sup> and 25 chronic asthmatics with low serum Mg with a mean±SD of 0.69±0.04 mmol·L<sup>-1</sup> (table 1).

The prevalence of hypomagnesaemia was found to be 27%. The number of hospitalizations in chronic asthmatics with low Mg (40%) was significantly higher than found in chronic asthmatics with normal Mg (11.8%), (p=0.04). Mean duration of asthma in chronic asthmatics with low Mg was (8.4±7.3 yrs) slightly shorter than in chronic asthmatics with normal Mg (10.3±10.6 yrs) however, this was not significant. In an univariate analysis, a higher proportion of severe asthma (28%) was found in chronic asthmatics with low Mg compared with normal Mg levels (12%), although this was not significant (table 1). In patients with hypomagnesaemia, there were more hospitalizations in patients categorized as severe asthmatics, compared to moderate and mild asthmatics (85%, 23%, 20% respectively, p<0.05).

Among β-agonist users, the proportion who used it < once per day, every day, or more than recommended, did not differ significantly between patients with normal Mg compared to patients with low Mg. In addition, the proportion that used inhaled steroids and theophylline therapy in both groups did not differ significantly. Multiple logistic regression analysis was performed to adjust for

Table 1. – Characteristic features of bronchial asthmatics (BA) with normal and low magnesium (Mg) levels

	BA with normal Mg	BA with low Mg	p-value
Patients n	68	25	
Serum Mg level mmol·L <sup>-1</sup>	0.82±0.08	0.69±0.04	
Serum albumin level mmol·L <sup>-1</sup>	44.8±4.2	45.0±3.7	NS
M/F	13/55	2/23	NS
Age yrs	40.8±13.9	36.8±10.3	NS
Duration of asthma yrs	10.3±10.6	8.4±7.3	NS
Number of hospitalizations	8/68 (11.8%)	10/25 (40%)	0.01
Severity of asthma			
Mild	39 (57%)	13 (52)	
Moderate	21 (31%)	15 (20%)	
Severe	8 (12%)	7 (28%)	NS
PEF	317.5±98.4	306.4±112.2	NS

NS: not significant; PEF: peak expiratory flow; M: male; F: female.

Table 2. – Multiple logistic regression coefficients and calculated adjusted odds ratio (OR) estimates with 95% confidence interval (CI) for risk factors associated with hypomagnesaemia among asthmatics

Variables	Coefficient	SEM	p-value	OR	95% CI
Age yrs	-0.0308	0.0230	0.181	0.97	0.925–1.015
Sex	-0.9903	0.8998	0.271	2.69	0.926–4.454
Duration BA	-0.0289	0.0348	0.406	0.97	0.902–1.038
Severity BA	0.9087	0.4432	0.040	2.48	1.611–3.349
β-agonist use	-0.2615	0.6292	0.678	0.77	-0.463–2.003
Steroid use	0.0058	0.7377	0.994	1.01	-0.436–2.456
K	-1.7992	0.9393	0.055	0.17	-1.671–2.011
P	-1.9492	1.2121	0.108	0.14	-2.236–2.516
Ca	2.0992	2.4226	0.386	8.16	3.412–12.908

BA: Bronchial asthma; K: potassium; P: phosphorus; Ca: calcium.

confounding variables and to identify important risk factors associated with hypomagnesaemia among chronic asthmatics (table 2). Severity of asthma was the only variable with a statistically significant odd ratio (OR) of 2.48 (95% CI 1.65–3.35). This means that among chronic asthmatics severe asthma is more likely to be associated with hypomagnesaemia than mild and moderate asthma. Other variables did not contribute significantly to the model.

### Discussion

In this study, which was performed on 93 chronic stable asthmatics, three important results were found. Firstly, the prevalence of hypomagnesaemia was up to 27%; secondly, chronic asthmatics with low Mg had a higher incidence of hospitalization; and finally, chronic asthma with low Mg was associated with more severe asthma.

The effects of hypomagnesaemia on asthmatics are not yet well defined. Most of the previous studies concentrated mainly on the use of Mg sulphate as a bronchodilator in β-agonist resistant asthma [9–15]. A few studies on animals showed that Mg has a protective effect on respiratory airways through different mechanisms of actions that lead to relaxation of airway smooth muscle and bronchodilatation of asthmatic airways [3–5]. Some reports showed an association between Mg deficiency and an increased airway hyperreactivity and pulmonary vascular resistance [1, 2].

Hypomagnesaemia is probably the most common under-diagnosed electrolyte disturbance in medical practice. Its prevalence in hospitalized patients is variable and may range from 4.6–47% depending on the type of population studied [24, 25]. The highest prevalence of hypomagnesaemia was reported for patients in intensive care units, reaching up to 65%. Its prevalence in most respiratory disorders including asthma was unknown. In a previous study by ROLLA *et al.* [19] on 95 patients with chronic obstructive airway disease, the prevalence of hypomagnesaemia was found to be 11%. In acute asthma, studies have shown conflicting reports on the prevalence of hypomagnesaemia [6, 8]. The prevalence of hypomagnesaemia found in the present study was unexpectedly high. However, a higher prevalence was observed in an earlier report by HAURY *et al.* [6] who found 50% of the 26 patients with acute asthma had hypomagnesaemia. In contrast to this, FALKNER *et al.* [8] found that serum Mg

level in 23 patients with acute asthma was similar to the 15-control nonasthmatic subjects [8]. In both studies, however, the total number of asthmatics studied was too small to draw a clear conclusion about prevalence of hypomagnesaemia among asthmatics. In addition, the purposes of these two studies were mainly to evaluate the effect of Mg sulphate as bronchodilator, rather than to evaluate the prevalence of hypomagnesaemia among asthmatics. Recently, DE VALK *et al.* [26] also found no difference in the serum, and red cell Mg levels between 20 mild asthmatics and 20 normal control subjects. However, this may have been due to the fact that all the asthmatics had mild asthma and the total number was also small.

There has been no previous study to evaluate whether low serum Mg can trigger acute asthma or is associated with increased frequency of hospitalizations, in chronic, stable asthmatics. In this study a statistically significant higher incidence of acute asthma and hospitalization reaching up to 40% was found in chronic asthmatics with low Mg compared to 11.8% in chronic asthmatics with normal Mg,  $p < 0.01$ . However, it is not clear why chronic asthmatics with low Mg have a higher incidence of hospitalizations. One possible explanation is that low serum Mg may increase airway hyperreactivity, and hyperresponsiveness that renders chronic asthmatics with low Mg more prone to developing bronchoconstriction and acute exacerbations of asthma. This may occur through either increased production of acetylcholine at cholinergic nerve endings [4] or through increased histamine release from mast cells [5], or may be through increased Ca flux into airways smooth muscle cells [27, 28]. In addition, there may be other possible unknown mechanisms by which hypomagnesaemia may cause bronchoconstriction and consequently increase the incidence of hospitalization among chronic asthmatics.

In the present study, measurements of serum Mg levels were performed in asthmatics with mild to severe asthma, where levels were found to be low, and which correlated significantly with severity of asthma,  $p < 0.04$ . By reviewing the literature, there has been no previous study that investigates the correlation between low serum Mg level and severity of asthma. EMELYANOV *et al.* [29] found a correlation between airway hyperreactivity and lower red cells Mg levels in asthmatics when compared with normal subjects. This was attributed to the low Mg intake in asthmatics. The correlation between low red cell Mg level and severity of asthma was not attempted in their study,

which could be an additional factor along with nutritional causes to explain the low red cell Mg level in asthmatics.

In previous studies, the occurrence of hypomagnesaemia in the management of acute asthma has been attributed to the use of  $\beta$ -agonists either orally [30] or intravenously [18] or by nebulization [21]. In the present study all the subjects studied were chronic, stable asthmatics and none were on oral, intravenous or nebulized  $\beta$ -agonist. They were also not on oral steroid therapy, or recently discharged from hospital, during measurements of serum Mg level, so its unlikely that low serum Mg levels were due to the effect of therapy received in hospital. Multiple logistic regression analysis showed that there was no association of hypomagnesaemia with inhaled  $\beta$ -agonists, inhaled steroids, theophylline therapy, K, Ca, or P in chronic asthmatics. Therefore, it is not known which factor is responsible for the hypomagnesaemia in chronic asthmatics.

Recently, an association between dietary Mg intake and the occurrence of asthma was shown. BRITTON *et al.* [16] found that low dietary Mg intake was associated with increased incidence of airway hyperreactivity, wheeze, and impairment of lung function in normal subjects. HILL *et al.* [7] found that high Mg intake ( $400 \text{ mg}\cdot\text{day}^{-1}$ ) in 20 asthmatics was associated with significant improvement of asthma symptom scores, though there was no significant improvement in FEV<sub>1</sub>, provocative dose of methacholine causing a 20% fall in FEV<sub>1</sub> (PD<sub>20</sub>), PEF variables, or decrease of bronchodilators used. However, the duration of Mg administration may be too short to detect any improvements in their pulmonary functions. Therefore, in this present study, the possibility of low Mg intake causing hypomagnesaemia cannot be ruled out and the dietary pattern in asthmatics may need to be investigated. It is possible that severe asthmatics may have more nutritional deficiencies than mild asthmatics and consequently may have lower Mg levels. However, further studies are needed to clarify these speculations.

In this study, the serum Mg level was only used to evaluate the presence of hypomagnesaemia in chronic asthmatics because of its availability in KAUH institution. Although, it may not reflect accurately the total body Mg store, it was found to be significantly reduced in asthmatics. Additional measurement of Mg level, either in the red cells, leukocytes or in the urine would have probably strengthened the findings if levels were also found to be low in asthmatics. These tests, however, are difficult to perform and are available only in specialized centres. The absence of a healthy control group was another drawback in this study. But the difference between normal and low Mg is still potentially relevant even with a different cut-off between normal and hypomagnesaemia in chronic asthmatics.

In summary, this study performed in chronic stable asthmatics, showed a high prevalence of hypomagnesaemia. Hypomagnesaemia was associated with significantly higher incidence of hospitalizations and correlated with severe asthma. The cause of hypomagnesaemia in chronic asthmatics remains unclear. Whether Mg supplementation in asthmatics with hypomagnesaemia has a role in controlling asthma should be studied.

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